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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,011	06/20/2003	Ciaran N. Cronin	SYR-AIK-5001-C1	5098

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TAKEDA SAN DIEGO, INC.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,011	CRONIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Appendix A

DETAILED ACTION

Status of the Application

[1] Claims 1-25 are pending in the application.

[2] Applicant's amendment to the claims, filed on 1/31/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[3] Applicant's election with traverse of Group I, claims 1-17, in the response filed on 1/31/2006 is acknowledged. The traversal is on the ground(s) that Groups I-II are related to a protein having at least 90% identity to residues 126-388 of SEQ ID NO:1. This is not found persuasive because, as noted in the prior Office action, the product of Group I can be used for a materially different process, *e.g.,* production of antibodies, which is undisputed by applicant. Further, each of Groups I and II requires a separate search because the claims of each invention recite unique limitations, *e.g.,* the invention of Group II requires a search for a method step of rational drug design using structural coordinates, which is not required for the search of Group I.

The requirement is still deemed proper and is therefore made FINAL.

[4] Claims 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 1/31/2006.

Priority

[5] Applicant's claim for domestic priority under 35 USC § 119(e) to US provisional application 60/390,355, filed on 6/21/2002, is acknowledged. The claims of this application appear to be supported by the priority document.

Information Disclosure Statement

[6] The examiner can find no information disclosure statement (IDS) in the application file. If the examiner has inadvertently overlooked an IDS that has been filed in the instant application, applicant's cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Drawings

[7] The drawings are objected to because Figure 3 is not numbered in accordance with 37 CFR 1.84(u)(1), which states, "[p]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter." A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

[8] Claims 1-3, 9-11, and 16-17 are objected to as reciting the improper sequence identifier "SEQ. ID No.," which should be replaced with "SEQ ID NO:". See 37 CFR 1.821(d).

[9] Claims 2-6 and 10-15 are objected to in the recitation of "[a] composition" and "[a] method" because the claims depend from a singular composition or method and should refer to the composition or method as "[t]he composition" and "[t]he method." Appropriate correction is required.

[10] Claims 7-8 are objected to in the recitation of "AIK". Abbreviations, unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[11] Claim(s) 4, 7-8, 12, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 4 and 12 are indefinite in the recitation of "resolution greater than 3.0 Angstroms" as it is unclear as to whether the term "greater than" is meant to be interpreted as meaning a higher resolution, *i.e.,* less than 3.0 Angstroms, or whether the term is meant to be interpreted as meaning a number of Angstroms greater than 3.0, *i.e.,* a lower resolution. It is suggested that applicant clarify the meaning of the claims.

[b] Claims 7-8 are indefinite in the recitation of "AIK" as neither the specification nor the claims teach which identifying characteristics distinguish an "AIK" polypeptide from other kinases. The application teaches many properties of an "AIK" polypeptide (beginning at p. 12) but fails to define which of these are necessary for inclusion of a kinase within the scope of the claims. It is suggested that applicant clarify the meaning of the term "AIK."

[c] Claim 16 is confusing in the recitation of "protein expressed as SEQ. ID No. 2" as SEQ ID NO:2 is a nucleic acid and not a protein. It is suggested that applicant replace the term with, for example, "protein encoded by SEQ ID NO:2." In the interest of advancing prosecution, the examiner has interpreted the term as meaning protein encoded by SEQ ID NO:2.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claim(s) 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-15 are drawn to a composition comprising a genus of protein crystals of amino acids 126-388 SEQ ID

NO:1 or variants thereof, a composition comprising a genus of crystalline AIK polypeptides having any amino acid sequence and a specific space group or unit cell dimensions, and methods of making said crystals. Claim 16 is drawn to a genus of compositions comprising at least a portion of a protein expressed as SEQ ID NO:2.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose even a single representative species of the genus of claimed crystals. While it is noted that the specification discloses a crystal of purified SEQ ID NO:3 (cleaved with rTEV protease) in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6), which is crystallized according to the method disclosed at p. 48, ¶¶[00198] and [0199] of the specification, the specification fails to adequately describe even a single representative species of the genus of protein crystals because there is no disclosure of

the angles between vectors a, b, and c of the crystal, *i.e.,* angles α, β, and γ. At the time of the invention, it was well-known in the art that the structure of a protein crystal was defined by three repeating vectors a, b, and c, with angles α, β, and γ, between them. See, *e.g.,* pp. 586 and 2725 of the "Encyclopedia of Molecular Biology" (Creighton, T., John Wiley and Sons, Inc. New York, 1999). See, *e.g.,* Cheetham et al. (US Patent Application Publication 2005/0143402) at pp. 20-21 and Anderson et al. (WO 03/031606) at p. 126, which disclose crystals of Aurora-2, which lists angles between vectors a, b, and c. In this case, the specification fails to describe even a single representative species of the genus of compositions comprising a protein crystal, which encompasses widely variant species, including crystals of polypeptides that are widely variant in amino acid sequence and/or function that are unliganded or having any bound ligand, wherein the crystals have any space group, and/or any unit cell dimensions and essentially any method of crystallization.

Regarding the genus of compositions of claim 16, the specification discloses only a single representative species of such compositions, *i.e.,* a composition comprising the polypeptide encoded by SEQ ID NO:2. Other than this single representative species, the specification fails to disclose any additional species of the genus of compositions, which encompasses any "portion" of a protein encoded by SEQ ID NO:2, including single amino acids and proteins that have any functionality, including non-functional polypeptides.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear,

concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of purified SEQ ID NO:3 (cleaved with rTEV protease) in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å, which is crystallized according to the method disclosed at p. 48, ¶¶[00198] and [0199] of the specification (claims 1-15) and a composition comprising the polypeptide encoded by SEQ ID NO:2, does not reasonably provide enablement for all crystals and methods of crystallization as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on

the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1-15 are so broad as to encompass: 1) crystals of polypeptide variants of amino acids 126-388 of SEQ ID NO:1 as encompassed by the claims having any function that are unliganded or have any bound ligand, wherein the crystals have any space group, and/or any unit cell dimensions and 2) essentially any method of crystallization thereof. Claim 16 is so broad as to encompass any "portion" of a protein encoded by SEQ ID NO:2, including single amino acids and proteins that have any functionality, including non-functional polypeptides. The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of purified SEQ ID NO:3 (cleaved with rTEV protease) in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å, which is crystallized according to the method disclosed at p. 48, ¶¶[00198] and [0199] of the specification and a composition comprising the protein encoded by SEQ ID NO:2.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal or for making a protein variant with an expectation that it maintains the desired activity/utility. Regarding the claimed crystal composition and method of making, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered

crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). While the references of Cheetham et al. (US Patent Application Publication 2005/0143402) and Anderson et al. (WO 03/031606) teach crystallization of AIK (referred to as Aurora kinase in these references), the polypeptide and crystallization parameters used were different, resulting in different crystals having different space groups and unit cell dimensions (see particularly pp. 20-21 of Cheetham et al. and p. 126 of Anderson et al.). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other

AIK polypeptides optionally having a desired space group and unit cell dimensions as encompassed by the claims can be achieved using *any* crystallization parameters as encompassed by the claims. Regarding the protein of the composition of claim 16, the reference of Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that even a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses the utility of the claimed crystal is in the determination of the 3-D structure of AIK (p. 2, ¶[0006]), which, as acknowledged by Branden et al. at p. 374, requires a diffraction-quality crystal. In this case, the specification discloses only a single working example of such a diffraction quality crystal and method of making thereof, *i.e.,* a crystal of purified SEQ ID NO:3 (cleaved with rTEV protease) in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å, which is crystallized according to the method disclosed at p. 48, ¶¶[00198] and [0199] of the specification. Other than this single working example of a crystal or method for making, the specification fails to provide guidance for crystallizing other polypeptides as encompassed by the claims with an expectation of obtaining diffraction-quality crystals optionally having the recited space group and/or

unit cell dimensions. It should be noted that the claims encompass crystals of mutant and variant AIK polypeptides and the specification fails to provide guidance for using those crystals that do not represent biologically relevant AIK polypeptides. Similarly, the specification discloses only a single working example of a polypeptide encoded by SEQ ID NO:2, *i.e.*, SEQ ID NO:3. Other than this single working example, the specification fails to disclose guidance for making and using other polypeptides that have the desired activity/utility of AIK.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all polypeptides having a substantial number of modifications as encompassed by the claims for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims and to determine those polypeptide structures that represent biologically-relevant AIK structures. Also, while methods of generating variants of a given polynucleotide, *e.g.*, mutagenesis, and methods of isolating homologous polynucleotides, *e.g.*, hybridization, were known, it is not routine in the art to screen for *all* polynucleotides having a substantial number of substitutions or modifications and encoding polypeptides having *any* function, as encompassed by the instant claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would

be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

[14] Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Sigma Chemical 1993 Catalog. Claim 16 is drawn to a composition comprising at least a portion of a protein encoded by SEQ ID NO:2. In this case, a "portion" of SEQ ID NO:2

can be interpreted as meaning a single amino acid of the protein encoded by SEQ ID NO:2.

Sigma teaches a Gly-Gln peptide (p. 1089, product ID G5149), which is a "composition," *i.e.,* a peptide, comprising an amino acid of the protein encoded by SEQ ID NO:2, *i.e.,* glycine or glutamine. This anticipates claim 16 as written.

[15] Claims 1-4, 9-12, and 15-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Cheetham et al. (US Patent Application Publication 2005/0143402).

The claims are drawn to a composition comprising a protein in crystalline form, wherein the protein has at least 90% identity to amino acids 126-388 of SEQ ID NO:1, optionally wherein the crystal diffracts x-rays to a resolution greater than 3.0 Angstroms, a method for making said crystal, and a composition comprising at least a portion of a protein encoded by SEQ ID NO:2.

Cheetham et al. teaches crystals of Aurora-2 in complex with an inhibitor that diffract x-rays to a resolution of 2.7 Angstroms (pp. 20-21, Example 9) and a method for making said crystals (p. 18, Examples 2-3). The Aurora-2 polypeptide used in the crystallization is amino acids 107-403 of SEQ ID NO:1 of Cheetham et al., which is 100% identical to SEQ ID NO:1 herein (see Appendix A). Cheetham et al. further teaches using the crystals to produce an X-ray diffraction pattern to determine the 3-D structure of the crystallized protein (p. 18, Example 4). This anticipates claims 1-4, 9-12, and 15-16 as written.

Conclusion

[16] Status of the claims:

- Claims 1-25 are pending.
- Claims 18-25 are withdrawn from further consideration.
- Claims 1-16 are rejected.
- Claim 17 is are objected to.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

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       SEQ1-126-388 (1-263)
       US-10-979-375-1 Sequence 1, Application US/10979375

Initial Score     =    263  Optimized Score  =    263  Significance =  0.00
Residue Identity =   100%  Matches          =    263  Mismatches   =     0
Gaps              =      0  Conservative Substitutions               =     0

                                                      X       10        20
                                                      RQWALEDFEIGRPLGKGKFGNV
                                                      ||||||||||||||||||||||
    QKQLQATSVPHPVSRPLNNTQKSKQPLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRPLGKGKFGNV
       80         90        100        110        120     X 130       140

            30         40         50         60         70         80         90
    YLAREKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVY
    |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
    YLAREKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYFHDATRVYLILEYAPLGTVY
    150        160        170        180        190        200        210

       100        110        120        130        140        150        160
    RELQKLSKFDEQRTATYITELANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCG
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
    RELQKLSKFDEQRTATYITELANALSYCHSKRVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCG
  220        230        240        250        260        270        280        290

     170        180        190        200        210        220        230
    TLDYLPPEMIEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDLISRL
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
    TLDYLPPEMIEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEGARDLISRL
          300        310        320        330        340        350        360

   240        250        260  X
    LKHNPSQRPMLREVLEHPWITANSS
    |||||||||||||||||||||||||
    LKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESASKQS
        370        380        390        400
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